REMARKS

Claims 1-3 and 5-21 are pending in the present application. Claims 4 and 22 were previously withdrawn from consideration subsequent to a restriction requirement. Claims 1 and 14 have been amended.

Applicants request that the Examiner call their attorney, Melanie McPeek Goddard, at 215-979-1310, for a personal interview, prior to issuing a further action in this application.

Claim Rejection under 35 U.S.C. § 102

The Final Office Action rejects claims 1, 5-15 and 17-20 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,851,527 to Hansen. This ground of rejection is respectfully traversed.

Claim 1 has been amended to recite a method for the in-vivo localization of water-insoluble molecules within a solid tumor comprising administering a water-soluble prodrug molecule to an animal, wherein said prodrug is a substrate to said enzyme and is hydrolyzed by said enzyme molecules present within the tumor, and wherein said hydrolysis forms a water-insoluble drug precipitate which is trapped within the extracellular space of the solid tumor.

Hansen discloses injecting a mammal with an enzyme-antibody conjugate and thereafter injecting the mammal with a soluble substrate-agent conjugate which is capable of transformation by the enzyme to form a product comprising the agent, which accumulates at the target site for treatment and/or diagnosis. The enzyme can transform molecules or subunits of the substrate-agent conjugate to liberate molecules of product in a form which will accrete at the target site due to favorable partition between the fluid bathing the target site and the tissue or other antigen-containing medium at the site itself. Hansen does not teach or suggest that hydrolysis of the conjugate by the enzyme forms a water-insoluble drug precipitate which is trapped within the extracellular space of a solid tumor. In the Advisory Action dated October 6, 2003, the Examiner states that Hansen teaches that its free drug is deposited on the cell membrane surrounding the cells and that deposition is a synonym for precipitation. However, a

substance may be deposited without being a precipitate, such as where an antibody is deposited into a tumor by its binding to an antigen. As indicated in the dictionary definition of "precipitate", attached hereto, a precipitate is "a solid or solid phase separated from a solution". Although Hansen discloses that its free drug is rendered significantly less soluble or is converted to a relatively poorly soluble drug, it does not teach that such drug precipitates, and further "less soluble" and "poorly soluble" are not synonymous with "insoluble", as required by claim 1. Further, none of the examples given by Hansen reveal a free drug that would precipitate under the conditions taught therein. Therefore claim 1 should be allowable over the Hansen reference. As claims 2-3 and 5-22 depend from claim 1, they should be allowable for the same reason.

The Final Office Action rejects claims 1, 5-15 and 20 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 6,361,774 to Griffiths et al. This ground of rejection is also respectfully traversed.

Griffiths et al. disclose pretargeting an enzyme to a mammalian target site and administering a cytotoxic drug in an initially detoxified prodrug form, which is converted to the more toxic drug in situ by the enzyme. Griffiths et al. do not teach or suggest that hydrolysis of the prodrug by the enzyme forms a water-insoluble drug precipitate which is trapped within the extracellular space of a solid tumor as required by claim 1. Rather, Griffiths et al. disclose a "less soluble drug" (column 7, lines 20-23) or "poorly soluble" drug (column 8, lines 19-23) which is deposited or remains in the vicinity of the target site. For these reasons, claim 1 should be allowable over Griffiths et al. As claims 5-15 and 20-22 depend from claim 1, they should be allowable for the same reason.

Claim Rejection under 35 U.S.C. § 103

The Action rejects claims 1-3 and 5-20 under 35 U.S.C. 103(a) as being unpatentable over Hansen in view of U.S. Patent No. 4,975,278 to Senter et al., U.S. Patent No. 6,495,553 to Shepard and further in view of U.S. Patent No. 6,265,427 to Camden, U.S. Patent No. 6,156,739 to Griffen et al., and U.S. Patent No. 5,854,968 to Horwitz et al. This ground of rejection is respectfully traversed.

Senter et al. fail to cure the deficiency of Hansen with respect to the limitation of a water-insoluble drug precipitate which is trapped within the extracellular space of a solid tumor. Senter et al. discloses a method for delivering cytotoxic drugs to tumor cells by the administration of a tumor-specific antibody-enzyme conjugate and the additional administration of a prodrug this is converted at the tumor site, in the presence of the antibody-bound enzyme, to an active cytotoxic drug. Senter et al. states that the "drug is . . .activated extracellularly and can diffuse into all of the tumor cells at that site". Thus, Senter et al. cannot teach or suggest a water-insoluble drug precipitate which is trapped within the extracellular space of the solid tumor.

Shepard also fails to cure the deficiency of Hansen with respect to the limitation of a water-insoluble drug precipitate which is trapped within the extracellular space of a solid tumor. Shepard discloses methods and examples of molecules for selectively killing a pathological cell by contacting the cell with a prodrug that is a selective substrate for an endogenous, intracellular enzyme. The prodrug is subsequently converted to a cellular toxin. Shepard deals with chemotherapeutic agents which are necessarily internalized into the cell and directly act upon a cell component. Thus, Shepard does not teach or suggest a drug which precipitates and is trapped within the extracellular space of a solid tumor.

Camden also fails to cure the deficiency of Hansen with respect to the limitation of a water-insoluble drug precipitate which is trapped within the extracellular space of a solid tumor. Camden discloses a method of treating leukemia using a benzimidazole derivative compound or a prodrug form of such compound. Camden does not teach or suggest that such compound precipitates upon hydrolysis of an enzyme and is thereafter trapped within the extracellular space of a solid tumor.

Griffin et al. disclose phosphate derivatives of quinazolinone compounds useful as prodrugs for providing active PARP inhibiting substances for medical use in conjunction with a cytotoxic drug or radiotherapy. These compounds are water soluble and necessarily go into the cells as PARP is intracellular. There is no teaching or suggestion of a water-insoluble drug precipitate, which is trapped within the extracellular space of a solid tumor. Rather Griffin et al. suggest a quinazolinone compound having greater aqueous solubility and that such compound may be effective in interfering with intracellular DNA repair mechanisms.

Horwitz et al. disclose a process for producing substantially impurity-free Bi-213 cations. There is no teaching or suggestion whatsoever of a water-insoluble drug precipitate which is trapped within the extracellular space of a solid tumor. Therefore, Horwitz et al. likewise fails to cure the deficiency of Hansen with respect to this limitation of claim 1.

Thus, as no cited reference, whether singly or in combination, teaches or suggests a prodrug hydrolyzed by enzyme molecules present within the tumor, wherein the hydrolysis forms a water-insoluble drug precipitate which is trapped within the extracellular space of the solid tumor, claim 1 should be allowable over these references. As claims 2-3 and 5-22 depend from claim 1, they should be allowable for the same reason.

Claims 1, 5-15 and 20-21 were rejected under 35 U.S.C §103(a) as being unpatentable over Hansen and Griffiths et al. in view of Griffin et al., and U.S. Patent No. 4,107,285 to Christenson and U.S. Patent No. 5,756,502 to Padia. This ground of rejection is also traversed.

Hansen, Griffiths et al., and Griffin et al., and the deficiencies with respect thereto, have been discussed above. Christenson discloses an improved radiolabelled derivative of a methaqualone analog used in the practice of a radioimmunoassay. There is no teaching or suggestion in Christenson that hydrolysis of a prodrug conjugate by an enzyme forms a water-insoluble drug precipitate which is trapped within the extracellular space of a solid tumor, and therefore Christenson fails to cure the deficiency of the above references with respect to claim 1.

Padia teaches quinazolinone derivatives useful for suppressing appetite, reducing gastric acid secretion and the like. There is no teaching or suggestion in Padia of hydrolysis of a prodrug by an enzyme which forms a water-insoluble drug precipitate which is trapped within the extracellular space of a solid tumor, and thus Padia also fails to cure the deficiency of the cited references with respect to claim 1.

Therefore, as none of the cited references, whether alone or in combination, teach or suggest each of the limitations of claim 1, this claim should be allowable. As claims 5-15 and 20-21 depend from claim 1, they should be allowable for the same reason.

In view of the foregoing remarks and amendments, Applicant submits that this application is in condition for allowance at an early date, which action is earnestly solicited.

The Assistant Commissioner for Patents is hereby authorized to charge any additional fees or credit any excess payment that may be associated with this communication to deposit account **04-1769**.

Respectfully submitted,

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